REMARKS

The present invention is premised on the discovery that alkali metal carbonates and bicarbonates potentiate the analgesic effect of diclofenac by increasing the rate at which orally administered diclofenac enters the bloodstream. In order to take maximum advantage of this discovery, the inventors have prepared a powdered formulation of potassium diclofenac and potassium bicarbonate, and a bilayer fast/slow release tablet, that allows diclofenac to enter the bloodstream as quickly as possible after oral ingestion. All of the claims have been amended to require the powder and/or fast/slow tablet formulation dosage form, as disclosed in examples 1 and 5 of the application. After entry of the amendments, claims 20, 21, 23 and 29-68 are pending.

The Granger reference (EP 0 466 650) has received considerable attention in this prosecution and remains the only reference cited by the Patent Office against the pending claims. Granger prepared NSAID/metal salt formulations based upon his discovery that metal salts can reduce stomach ulcers caused by NSAIDS, and thus prepared his formulations for reasons that are much different than the reasons the current inventors prepared their diclofenac/alkali metal carbonate/bicarbonate formulations. Applicant's position on this issue has been argued previously and will not be repeated herein other than to point out the following additional deficiencies in the Granger reference.

I. The Granger reference does not disclose the claimed powder and/or fast/slow tablet formulation dosage form.

All of the claims in this application require that the pharmaceutical formulation be in the form of a powder and/or fast/slow tablet formulation that can be readily dissolved or dispersed in water and taken orally. This dosage form builds upon the nature of the claimed invention, and allows for even further rapid bioavailability of diclofenac, and the treatment of pain when such rapid bioavailability is desired (e.g. in migraine headaches.) By preparing the claimed formulation as a powder and/or fast/slow tablet formulation, the invention ensures that the diclofenac enters the bloodstream as quickly as possible after it is ingested, and allows for the treatment of these periodic acute pain episodes.

In contrast, the Granger reference is concerned with pain sufferers who suffer gastrointestinal problems because they take NSAIDs on a regular basis. Granger discloses that various metal bases and salts can buffer the effect of NSAIDs in these regular pain sufferers, and thereby prevent or minimize damage to their gastrointestinal tract. According to Granger, this buffered NSAID therapy should be employed "in a multiple dose regimen during long term therapy, as in the treatment of chronic inflammation," because this type of dosing regimen "can overwhelm the body's ability to adjust" to the inhibition of prostagiandin biosynthesis and cause painful stomach damage. (P. 1, lines 27-29.) Granger was not proposing therapy for patients who suffer period episodes of acute pain and need rapid onset of pain relief because, as Granger himself notes, "[d]amage to the stomach as a result of this inhibition of prostaglandin biosynthesis generally is minimal with individual doses." (P. 1, lines 26-27.)

The pharmaceutical dosage forms that Granger discloses are consistent with the chronic pain patient populations that he proposes to treat – i.e. "oral tablets, capsules, elixirs, syrups, suspensions, etc." (p. 3, lines 11-13). Granger does not disclose formulations that are designed to provide rapid onset of pain relief for periodic acute pain sufferers, and thus does not disclose the claimed powder and/or fast/slow tablet formulations. Therefore, his disclosure would not have motivated a skilled worker to make the claimed powder and/or fast/slow tablet formulations, and his disclosure neither anticipates nor renders obvious the claimed invention.

II. <u>The Granger reference does not disclose the claimed flavor enhancing combination.</u>

Independent claim 20 recites a pharmaceutical formulation that contains mint, aniseed or ammonium glycyrrhizinate as a flavoring agent. While the July 1, 2004, Office Action states that these flavoring agents are anticipated by the Granger reference – nowhere does Granger disclose any of these particular flavoring agents. Rather, Granger simply discloses that "sweetening and flavoring agents and preservatives can also be included where appropriate" (p. 3, lines 22-23), and specifically lists "natural sugars" and "corn sweeteners" as suitable excipients. (P. 3, line 18.) This meager disclosure does not include the claimed flavor enhancing combination, and does not anticipate the claimed pharmaceutical formulations.

III. The Granger reference does not inherently disclose the claimed T_{max} or C_{max} values.

Several independent claims also require that the claimed method achieve an average T_{max} between 5 and 30 minutes after administering the powder and/or fast/slow tablet formulation. Dependent claims require the C_{max} to exceed about 1700 ng/ml when 50 mg is administered. The Patent Office contends that these T_{max} and C_{max} properties are inherent in the formulations disclosed by Granger. However, a prior art disclosure can only anticipate by inherency if the claimed physical property is necessarily "the natural result flowing from the operations as taught" by the Granger reference. Mehl/Biophile Int. Corp. v. Milgraum, 192 F.3d 1362, 52 USPQ2d 1303 (CAFC 1999). Granger's formulations do not anticipate the claimed methods because his formulations would not necessarily have achieved these claimed pharmacokinetic properties. (Compare formulations B and C in Table 4, which were both powder formulations and achieved an average T_{max} 10 minutes after administration, with formulation A, a conventional immediate release tablet, which did not achieve average T_{max} until 30 minutes after administration; compare also formulation B, which did not contain an alkali metal bicarbonate and did not reach 1700 ng/ml C_{max}, with formulation C, which contained sodium bicarbonate, and did achieve the claimed C_{max}.)

Because the Granger reference does not disclose powder and/or fast/slow tablet formulation dosage forms, and because the Granger reference is not concerned with rapidly metabolizing diclofenac in the bloodstream at the concentrations claimed herein, it does not teach a formulation that results in rapid bioavailability of diclofenac, and the claimed T_{max} and C_{max} are not necessarily "the natural result flowing from the operations as taught" by the Granger reference. Mehl/Biophile Int. Corp. v. Milgraum, 192 F.3d 1362, 52 USPQ2d 1303 (CAFC 1999). Therefore, the Granger reference does not "inherently" anticipate the pending claims.

IV. The Granger reference does not disclose the claimed 20-80% metal alkali bicarbonate:diclofenac ratio.

The Patent Office also maintains that Granger discloses a buffer/NSAID ratio that overlaps the claimed 20-80% ratio based on Granger's statement on line 58 of page 2 that the buffer and NSAID can be administered at a ratio of 25 to 100%. However, Example 1 is the only example in the Granger reference that discloses human pharmaceutical formulations, and it

discloses buffer/NSAID ratios ranging from 167% (formulation 3) to 800% (formulation 1). The 25-100% range disclosed on page 2 does not encompass any of these three specific human formulations. A close reading of the Granger reference (as would be expected from a skilled worker) reveals that the 25-100% ratio recited on line 58 of page 2 is derived from the rat data in examples 2 and 3. Granger only discloses buffer/NSAID ratios for actual human pharmaceutical products that are at least 167%, and thus teaches ratios outside of the ratios claimed herein.

It is well accepted that a prior art reference must be evaluated for what it teaches those of ordinary skill in the art. See In re Boe, 355 F.2d 961, 148 USPQ 507 (CCPA 1966). A skilled worker would not prepare a 25-100% formulation for human administration based upon Granger's teachings because (1) Granger recommended much more conservative buffering ratios ranging from 167-800% when proposing actual human formulations in example 1, and (2) Granger's rat examples conducted with formulations at these ratios did not uniformly prevent ulcers (examples 2 and 3). Because the skilled worker would immediately recognize that Granger was proposing 25-100% for rat experiments, and that a much higher ratio would be needed for actual human formulations, the Granger reference does not anticipate the pending claims.

V. The Granger reference does not disclose the claimed diclofenac/metal bicarbonate combination.

The Granger reference also fails to disclose the diclofenac/alkali metal carbonate/bicarbonate combination claimed in this application because of the number of NSAID combinations disclosed in the Granger reference. Granger discloses thousands of combinations of NSAIDs and buffers, as shown below:

# of NSAIDS – 34 (p. 2 lines 10-22)
# of salts for NSAIDS – greater than 8 (p. 2, lines 52-56)
# of buffering agents – 5 (p. 2, line 48)
# of salts for buffering agents – 6 (p. 2, lines 48-49)

TOTAL # of combinations – greater than 8,000

Moreover, Granger generally teaches toward embodiments other those claimed herein. For example, (1) Granger does not exemplify a single use of diclofenac or a fenamic acid NSAID, preferring to use the indene and ibufenac derivatives, and (2) Granger expresses a preference for the use of sodium salt NSAIDs when the preferred salt claimed in this application is potassium (see Granger, p. 2 at line 56).

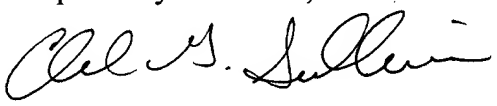
Anticipation only occurs if the skilled worker would "at once envisage" the claimed combination. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). The cases are clear that a skilled worker would not "at once envisage" a particular combination from a disclosure that recites more than 8,000 combinations, without a more focused disclosure of a subgenus in the reference. Compare In re Wilder, 429 F.2d 447, 155 USPQ 545 (CCPA 1970) (finding anticipation of a rubber/additive combination from a disclosure of 24 rubber additives and 2 types of rubber) with In re Ruschig, 343 F.2d 965, 145USPQ2d 274 (CCPA 1965) (no anticipation where prior art disclosed genus of 130 compounds), In re Arkley, 455 F.2d 586, 172 USPQ 524 (CCPA 1971) (no anticipation found where reference disclosed combinatorial reaction of 38 potential precursors and 15 tertiary amines) and In re Kollman, 595 F.2d 48, 201 USPQ 193 (CCPA 1979) (no anticipation found where prior art disclosed "many dozens" of compositions and failed to suggest the "required FENAC/diphenyl ether ratio").

The Patent Office has crafted a subgenus around Granger's disclosure of sodium bicarbonate in the examples. However, even this subgenus includes 272 species, when one considers the fact that Granger discloses 34 NSAIDs and 8 NSAID salts. Because it is illogical to believe that a skilled worker would "at once envisage" the claimed combination from this extremely large number of species, especially when the diclofenac is limited to the potassium salt, Granger does not anticipate the claimed invention.

CONCLUSION

For the above and foregoing reasons, a prompt notice of allowance is earnestly solicited. Should the Examiner have any further questions concerning this matter, he is invited to contact the undersigned at 404-572-3513. Please grant any additional extension of time required to enter this response and charge any additional fees, or credit any overpayment to Deposit Account No. 11-0980.

Respectfully submitted,



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